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A new prognostic index for overall survival in malignant pleural mesothelioma: the rPHS (regimen, PS, Histology, or Stage) index

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A prognostic index in malignant mesothelioma

ABSTRACT

Background

Existing prognostic indices (PI) for malignant pleural mesothelioma (MPM) do not incorporate the recent advances in oncology care. The purpose of this study was to provide a PI for overall survival (OS) in MPM patients treated with chemotherapy with pemetrexed (PEM) or best supportive care (BSC) in the recent clinical setting.

Methods

A retrospective cohort study was performed in two hospitals in Japan (2007 - 2013). The primary outcomes were OS. The Cox proportional hazards model was used for multivariable analyses to identify prognostic factors. A final model was chosen based on both clinical and statistical significance.

Results

A total of 283 patients (CTx: n=228, BSC: n=55) were enrolled in the study. On multivariate analysis, regimen including platinum plus PEM, a performance status > 0, non-epithelial histological type, and stage IV disease predicted poor OS in CTx patients. As hazard ratios of individual risk factors were approximately similar, a prognostic index for OS was constructed by counting the risk factors. Median OS in CTx patients decreased by each 1-point increase in this count: 1030 days for zero; 658 days for one;

373 days for two; 327 days for three; 125 days for four. Internal validation using the bootstrapping technique showed robustness of the model (c-index, 0.677; 95% Confidence Interval [CI], 0.624-0.729). Further, the discrimination was consistent in BSC patients (c-index, 0.799; 95% CI, 0.725-0.874).

Conclusions

This novel index can provide clinicians and MPM patients with a better framework for discussing prognosis at the time of diagnosis.

A mini-abstract:

We developed a new prognostic index for malignant pleural mesothelioma. The index reflects the recent real-world data. The index showed better discrimination than previous index.

Keywords:

Malignant pleural mesothelioma – pemetrexed - best supportive care - prognostic index - palliative care.

INTRODUCTION

Malignant pleural mesothelioma (MPM) used to be a rare malignancy of the mesothelium. In recent years, the incidence of this disease has increased, and this trend will likely continue worldwide over the next decade (1).

Despite recent advancements in treatment, surgery, radiotherapy and chemotherapy or multimodality therapy has not be proven to be curative (2–4) . For the majority of patients, treatment options are limited to palliative chemotherapy and best supportive care (BSC) (5).

In oncologic palliative care, early determinations of prognosis play an important role in guiding end-of-life care and efforts designed to improve patients' quality of life (6, 7).

To determine the prognosis of patients with MPM, four prognostic indices (PI) have been developed; one by the Cancer and Leukaemia Group B (CALGB) (8), and three by the European Organization for Research and Treatment of Cancer (EORTC) (9–11).

While the first two PIs from EORTC can indicate either a favorable or an unfavorable outcome, neither can predict the duration of survival, which means both are impractical when discussing life expectancy with a patient. The CALGB PI is complex to use, because it has various cutoffs to consider. Above all, these PIs are based on clinical trial data and may not be applicable to the clinical setting. Further, they do not incorporate

information regarding pemetrexed, which can improve overall survival (OS), and does not incorporate recent advancements in supportive care (3, 12–14). Therefore, while existing PIs might be useful for researchers in deciding which patients to include in clinical trials, these systems are less useful for clinicians who need to discuss prognoses with their MPM patients.

The purpose of this study was to provide a new PI for OS in MPM patients who underwent treatment with pemetrexed or best supportive care in a recent clinical setting.

Materials and methods

Study design and patients

A retrospective cohort study was performed, covering the period between April 1st, 2007 and March 31st, 2013. The cohort was defined as all patients with histologically proven (15) MPM at either one of two tertiary hospitals that serve the South Hanshin medical region, which is an area of high MPM incidence area in Japan (16).

Patients who had more than one cancer, underwent autopsy, or who received palliative chemotherapy without pemetrexed were excluded, Because our purpose is to develop a new PI in MPM patients who underwent treatment with pemetrexed which is the "standard of care" (5). Patients who had received chemotherapy or radiotherapy before

99 diagnosis, trimodal therapy, or surgical therapy extra-pleural pneumonectomy or
100 pleurectomy or decortication) were excluded to avoid confounding influences (17).
101
102 **Definitions of prognostic variables**
103 Potential prognostic factors that were analyzed included: histological subtypes (15),
104 International Mesothelioma Interest Group stage (18), chemotherapy regimen, age,
105 gender, Eastern Cooperative Oncology Group performance status (PS) (19), subjective
106 symptoms, smoking history, asbestos exposure history, comorbidities (Charlson score
107 (20)) and baseline blood or effusion parameters at the time of diagnosis.
108
109 **Primary outcomes measurement**
110 The primary outcome endpoint was OS, as defined by the length of time from the date
111 of diagnosis to death. Patients who had not died or who were lost to follow-up were
112 censored when they were last known to be alive before September 1st, 2013.
113
114 **Statistical analyses**

We developed the PI in those who were treated with chemotherapy to minimize the bias due to confounding by indication (21). We also evaluated the applicability of the PI in those that received BSC.

In derivation, step continuous and nominal prognostic variables were dichotomized according to previous studies (8, 9, 11, 21–27). OS was estimated using the Kaplan–Meier method. The log-rank tests for each prognostic factor were used for univariate analyses. The Cox proportional hazards model was used for multivariate analyses. The Akaike's information criterion (AIC), Schwartz's Bayesian information criterion (BIC), and Harrell's c index (c-index) were used for the discrimination of the model. A final model was chosen based on both clinical and statistical significance. We compared the discrimination of our index with the EORTC prognostic index (9) and the progression-free index of EORTC (11).

Calibration curves showing agreement between observed and predicted outcomes over a range of predicted probabilities were drawn. We also drew Cox-Snell residuals and measured Moreau, O'Quigley, and Lellouch statistics (28). We drew log-log hazards curves and tested the proportional hazard assumption. The bootstrapping technique was used for the internal validation (for 500 replications (29)).

We carried out sensitivity analysis using multiple imputation for variants with clinically significance. Two-sided p values < 0.05 were considered to indicate statistical significance. We used Stata® ver. 13.0 (Stata Corp., College Station, TX).

Ethical considerations

This study was performed according to the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Japanese Ministry of Health, Labour and Welfare. The protocol for the study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (E1883). The protocol was registered in the University Hospital Medical Information Network Clinical Trials Registry with the number: UMIN000011733.

Results

This study included 228 patients who were treated with chemotherapy with pemetrexed and 55 patients who received BSC (Figure 1). Patient characteristics are shown in Table 1. Survival curves for each group are shown in the Figure 2.

The median lengths of follow-up were 345.5 days for the chemotherapy group and 250 days for the BSC group. During the follow-up period, 161 patients (70.6%) died in chemotherapy group, and 40 patients (72.7%) died in the BSC group, respectively. Univariate survival analyses are also shown in Table 1. Fifteen parameters were significantly correlated with OS according to univariate analyses: asbestos exposure, PS, dyspnea, anorexia, chest pain, body weight (BW) loss, fever, histological type, Stage, Regimen, white blood cell (WBC), platelet (Plt) count, C-reactive protein (CRP), Lactate dehydrogenase (LDH**)**, and cytokeratin-19 fragment (CYFRA). Because of the theoretical collinearity of symptom variables, we chose only PS with respect to clinical relevance. We repeated the multivariate analysis while analyzing WBC, Plt, and CRP, separately, because of the collinearity of inflammatory variables. The discrimination for PS, Asbestos Exposure, Histology, Stage, Regimen, LDH, and CYFRA were 823 (AIC), 844 (BIC), and 0.714 (c-index). The discrimination for seven variables with WBC were 821 (AIC), 845 (BIC), and 0.726 (c-index). The discrimination for six variables with CRP were 825 (AIC), 849 (BIC), and 0.715 (c-index). The discrimination for six variables with Plt were 824 (AIC), 848 (BIC), and 0.711 (c-index). We entered WBC into a stepwise backward Cox proportional hazards model (Table 2). PS, histology, stage, and regimen remained significant after the

multivariate analysis. Hazard ratios of individual risk factors were 1.82-2.25. Therefore, a PI for the OS was constructed using a simple count of the number of risk factors (Table 3). The median OS of each category is shown in Table 4.

We calculated the discrimination of the rPHS (regimen, PS, Histology, or Stage) index. The c-index was 0.677. After 500 bootstrap replications from the original patients, the 95% confidence interval (CI) of the c-index of the PHS score was 0.624-0.729. We calculated the c-index for the EORTC prognostic index (9), which was 0.569. The difference between the two indices persisted after bootstrap replications (0.108; 95%CI, 0.053-0.163). We also calculated the c-index for the progression-free index of the EORTC (11), which was 0.552. The difference between the two indices persisted after bootstrap replications (0.125, 95%CI, 0.082-0.166).

There was good calibration of the model, with close agreement between observed and predicted OS (Figure S1), and also with close agreement between Cox-Snell residuals and the 45-degree slope (Figure S2). The Moreau, O'Quigley, and Lellouch test showed that the model fit of the Cox regression model was adequate ($p = 0.38$).

We drew log-log hazards curves for the CTx group which were parallel (Figure S3). The p value of the test for the proportional hazard assumption was 0.07.

We carried out sensitivity analysis using multiple imputation to create and analyze 10 multiply imputed datasets. We imputed only PS with regards to clinical significance. These estimates and their standard errors were combined using Rubin's rules (30). The results showed consistency (Table 4). The discrimination was also consistent in the BSC group (c-index, 0.799; 95%CI, 0.725-0.874).

Discussion

We developed a new PI for patients with MPM that predicts median OS, incorporates pemetrexed information, and incorporates recent advancements in supportive care in the normal clinical setting. The rPHS index is obtained by a simple count of the risk factors (regimen including platinum plus PEM, PS>0, non-epithelial histology, and stage>3). The index can stratify patients into four different prognostic groups with different median survivals. The index has good discrimination for those treated with pemetrexed group as well as those treated with BSC.

Patients with advanced cancer often want to know their prognosis (31). One study (32) reported that patients with advanced cancer have an overwhelming preference for an opportunity to prepare for the end of life. They want to know that their families are prepared for their death, which often includes having finances in order, and for patients,

having funeral arrangements planned. They want to have the opportunity to resolve unfinished business, remember personal accomplishments, and to say goodbye to important people. In order to allow these patients to direct their energies to these matters, it is important to provide them with accurate information regarding their prognosis. In fact, early palliative care, including early accurate perceptions of prognosis, has improved the quality of life and possibly the OS of patients with advanced cancer (6). We believe that the present findings will influence the usual care of MPM patients for several reasons. When one patient diagnosed with MPM and decided to treat with pemetrexed-regimen, the patient and their physician can discuss based on the median OS of the rPHS index. Without the index we discussed the prognosis based on the median survival time from the trial or the cohort study. Our PI consists of variables frequently used in usual care of MPM patients. Indeed, PS, histology, and stage are well-known prognostic factors in previous studies (8–11, 33) and are components of the evaluation at the time of initial diagnosis (34). Further, our PI can be calculated easily by simple counting; calculators are not necessary, and our PI has more discriminatory power than the EORTC PI (9), which is one of the best-known clinical PIs. We note that the distribution of median age and OS were different when comparing previous reports (8–11) and our CTx cohort; our study included more elderly patients

(67.7 versus 58-62 years), and our study included patients with relatively better prognoses (11.5 versus 5-12.6 months). The cohort of our study ensures the generalizability of the findings, because the two hospitals cover the South Hanshin medical region and any patients with MPM in this region will visit one of these two hospitals. So, the participants in the present study are a good representation of patients with MPM. We included only patients with histologically proven MPM and not those with only cytologically proven MPM. Because there is morphologic overlap between benign reactive mesothelial cells and malignant cells of mesothelioma (15), it is not recommended to make a diagnosis of mesothelioma based on cytology alone (34). We think that this restriction ensured our study result.

Our cohort consisted of patients treated with BSC. For the small number of BSC participants we didn’t develop another index for BSC patients, but validated PHS index. The discrimination was good (c-index, 0.799; 95% CI, 0.725-0.874). No previous study has validated a PI in patients treated with BSC. This information will be useful for discussions regarding prognosis between clinicians and their patients.

Since 1998, several PIs have been described. In contrast to our PHS index, other PIs were based on clinical trial data. Therefore, in the context of usual care, our PHS index might be more widely applicable than other PIs. We cannot compare our PI with the PI

of Bottomley (23) because we did not evaluate patients with the EORTC LC13 or QLQ-C30. Their PI's c-index was 0.66. The point estimation was similar to that of our PI. Pass (27) reported stage, histology, sex, age, treatment, adjuvant treatment, platelets and WBC are clinical prognostic factor except for PS. We think this discrepancy may reflect the difference of target population. We excluded those received surgery, but Pass's target population is those received either palliative or potentially curative surgery. There are several limitations in the study. First, this was a retrospective study with a substantial number of missing PS data, so we performed sensitivity analysis using multiple imputation. The result confirms the robustness of our model. Second, we were not able to know the reason why each patient treated with the modality because this is a retrospective study and treatment allocations were not protocol based. To clarify the preferences for treatment in MPM patients prospective qualitative and quantitative studies will be needed (36). But this limitation reflects the normal clinical setting. Third, we assessed internal validation with the bootstrap method, but the sample size of this study did not allow for external validation, so validation studies are needed.

We developed a new PI using PS, histology, and stage for MPM patients treated with chemotherapy or BSC. This PI will allow better discussion between clinicians and

patients with regards to prognosis. Further prospective studies using this PI are warranted.

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Conflict of interest statement

None declared.

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Table 1 Patient characteristics and results of univariate analyses of OS

Clinical factors	Chemotherapy (n = 228), N (%)	Median OS (days)	95%CI	p value	BSC (n=55), n (%)
Age (years) mean±SD	67.7±8.2				74.5±9.6
Age (years)					
75>	181 (79.4)	512	375-562	0.2000	24 (43.6)
75≤	47 (20.6)	366	190-441		31 (56.4)
Gender					
Female	39 (17.1)	514	314-699	0.4700	13 (23.6)
Male	189 (82.9)	432	359-524		42 (76.4)
Smoke					
Never	65 (30.0)	524	366-624	0.4100	19 (38.0)
Current / Ever	152 (70.0)	425	327-524		31 (62.0)
Missing	11				5
Charlson comorbidity index					
<2	205 (89.9)	461	372-533	0.5100	42 (76.4)
2≤	23 (10.1)	366	224-1213		13 (23.6)
Asbestos exposure					
No	28 (12.4)	710	327-1213	0.0480	
Yes	197 (87.6)	397	353-511		14 (26.4)
Missing	3				39 (73.6)
PS					2
0	37 (22.4)	926	524-1372	0.0014	
1≤	128 (77.6)	434	362-562		19 (41.3)
Missing	63				37 (58.7)
Dyspnea					9
No	52 (33.8)	658	524-1030	0.0003	13 (31.7)
Yes	102 (66.2)	425	319-512		28 (68.3)
Missing	74				14
Anorexia					
No	145 (82.4)	524	432-654	0.0001	29 (55.8)

Yes	31 (17.6)	296	166-373		23 (44.2)
Missing	52				3
Chest pain					
No	58 (39.2)	648	511-926	0.0007	16 (43.2)
Yes	90 (60.8)	353	263-432		21 (56.8)
Missing	80				18
BW loss					
No	96 (70.7)	566	512-804	0.0001	20 (60.6)
Yes	41 (30.0)	299	177-425		13 (39.4)
Missing	91				22
Fever					
No	92 (76.7)	524	397-648	0.0280	38 (92.7)
Yes	28 (23.3)	353	223-518		3 (7.3)
Missing	108				14
Histological type					
Epithelial	149 (65.4)	545	493-640	0.0000	17 (30.9)
Non-epithelial	79 (34.7)	277	221-330		38 (69.1)
Stage					
I-III	133 (58.3)	549	461-658	0.0000	30 (54.5)
IV	95 (41.7)	327	242-375		25 (45.5)
Regimen					
Platinum plus PEM	205 (89.9)	221	373-547	0.0007	
PEM monotherapy	23 (10.1)	499	86-425		
WBC (/μl)					
8300>	160 (70.5)	512	391-598	0.0400	36 (65.5)
8300≤	67 (29.5)	359	238-501		19 (34.5)
Missing	1				
Neutro/lymph					
5>	182 (82.4)	445	368-549	0.0600	35 (64.8)
5≤	39 (17.7)	362	188-514		19 (35.2)
Missing	7				1
Hb (g/dL)					
10≤	218 (96)	445	372-544	0.0700	45 (81.8)
10>	9 (4.0)	224	66-526		10 (18.2)
Missing	1				

Plt (10^5/μl)					
40>	188 (82.8)	461	373-549	0.0100	42 (76.4)
40≤	39 (17.2)	327	176-526		13 (23.6)
Missing	1				
ALP (IU/l)					
Abnormal	32 (14.9)	397	228-562	0.93	0 (0.0)
Normal	183 (85.1)	441	362-544		53 (100.0)
Missing	13				2
LDH (IU/L)					
Abnormal	26 (11.6)	493	375-544	0.011	11 (20.4)
Normal	198 (88.4)	242	87-603		43 (79.6)
Missing	4				1
CRP (mg/dl)					
5>	189 (83.3)	461	373-549	0.0076	40 (72.7)
5≤	38 (16.7)	359	167-518		15 (27.3)
Missing	1				
CEA (ng/ml)					
5>	200 (94.3)	338	156-NE	0.7800	45 (95.7)
5≤	12 (5.7)	441	366-526		2 (4.3)
Missing	16				8
CYFRA (ng/ml)					
3.5>	162 (75)	512	375-598	0.0090	22 (48.9)
3.5≤	54 (25)	368	242-445		23 (51.1)
Missing	12				10
Pleural glucose (mg/dl)					
40>	21(22.3)	511	156-710	0.2200	10 (30.3)
40≤	73(77.7)	373	319-547		23 (69.7)
Missing	134				22

Abbreviations: N, number; OS, overall survival; SD, standard deviation; CI, confidence interval; BSC, best supprotive care; PS, Eastern Cooperative Oncology Group performance status; BW, body weight; PEM, pemetrexed; WBC, white blood cell; Neutro, neutrocyte; Lymph, lymphocyte; Hb, hemoglobin; Plt, platelet; ALP, alkaly phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CYFRA, cytokeratin-19 fragment.

Table 2 Backward Cox proportional hazards model

Clinical factors	HR	95%CI
PS		
0	1	
1≤	2.40	1.36-4.23
Asbestos exposure		
no	1	
yes	1.64	0.75-3.58
Histological type		
Epithelial	1	
Non-epithelial	2.16	1.40-3.32
Regimen		
Platinum doublet	1	
Pemetrexed only	3.18	1.59-6.39
Stage		
I-III	1	
IV	1.57	1.03-2.39
LDH		
Normal	1	
Abnormal	1.46	0.71-2.99
CYFRA (ng/ml)		
3.5>	1	
3.5≤	1.10	0.69-1.76
WBC (/μl)		
8300>	1	
8300≤	1.56	0.99-2.45

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CYFRA, cytokeratin-19 fragment; WBC, white blood cell.

Table 3 Final model

Clinical factors	HR	95% CI	Score
PS			
0	1		1
1≤	2.06	1.22-3.44	
Histological type			
Epithelial	1		1
Non-epithelial	2.15	1.41-3.26	
Stage			
I-III	1		1
IV	1.82	1.23-2.69	
Regimen			
Platinum plus PEM	1		1
PEM monotherapy	2.25	1.16-4.36	

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, Eastern

Cooperative Oncology Group performance status; PEM, pemetrexed.

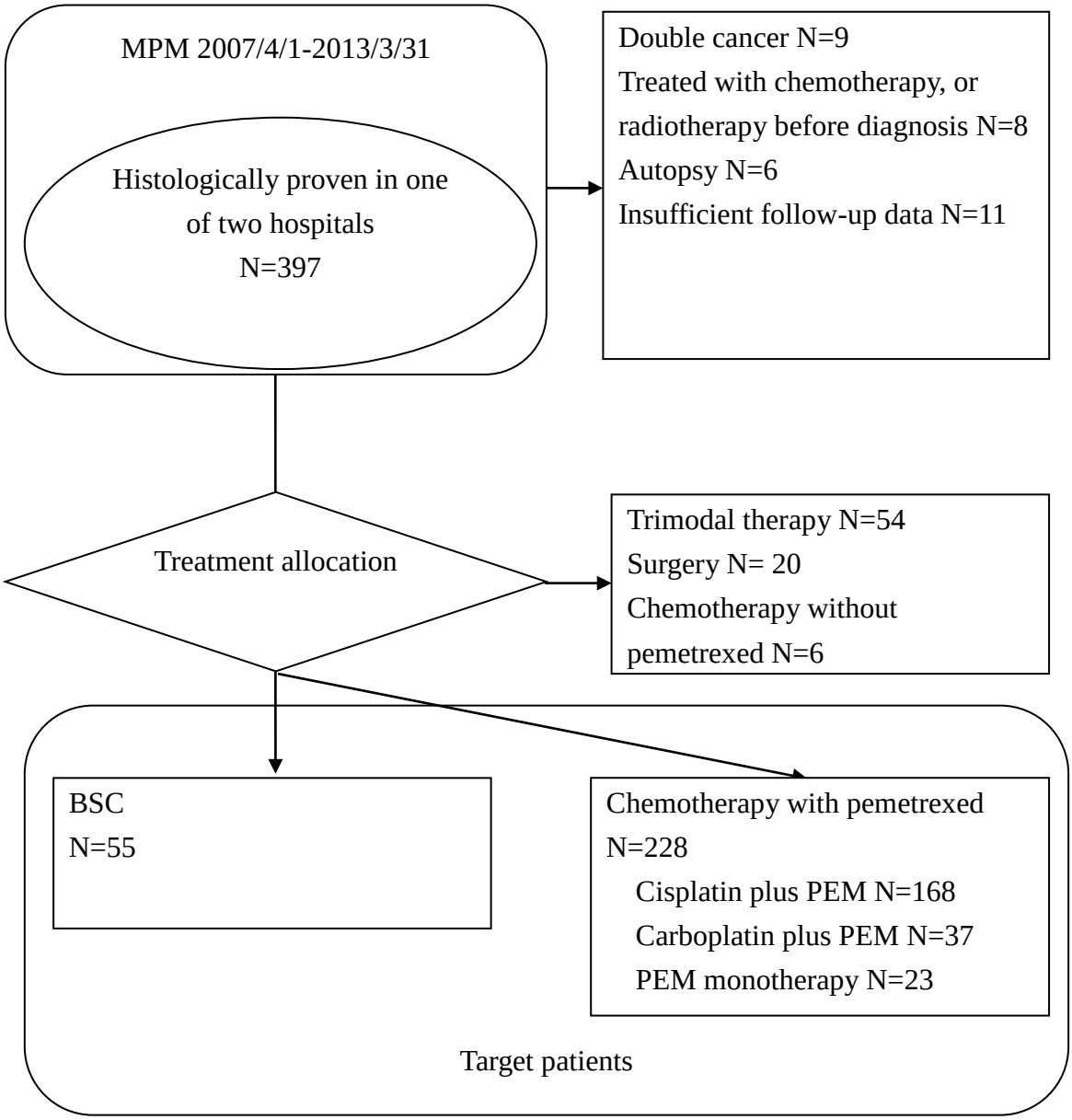
Table 4 The rPHS index for overall survival (sensitivity analysis)

	Chemotherapy			**Best supportive care**		
Score	**N**	**Median OS (days)**	**95% CI**	**N**	**Median OS (days)**	**95%CI**
0	24 (28)	1030 (926)	661-1399(598-1253)			
1	57 (76)	658 (603)	444-872 (458-678)	6 (7)	573 (573)	530-616 (477-669)
2	56 (79)	373 (367)	223-522 (305-429)	15 (20)	408 (402)	178-638 (221-583)
3	22 (39)	327 (240)	189-465 (133-347)	11 (20)	250 (94)	11-489 (0-228)
4	5(6)	125(48)	16-234(0-184)	6 (8)	26 (34)	0-103 (0-126)

rPHS index = (if platinum + PEM 0, otherwise 1) + (if PS 0<, otherwise 0) + (if Histology non-epithelial, otherwise 0) + (if Stage=4, otherwise 0)

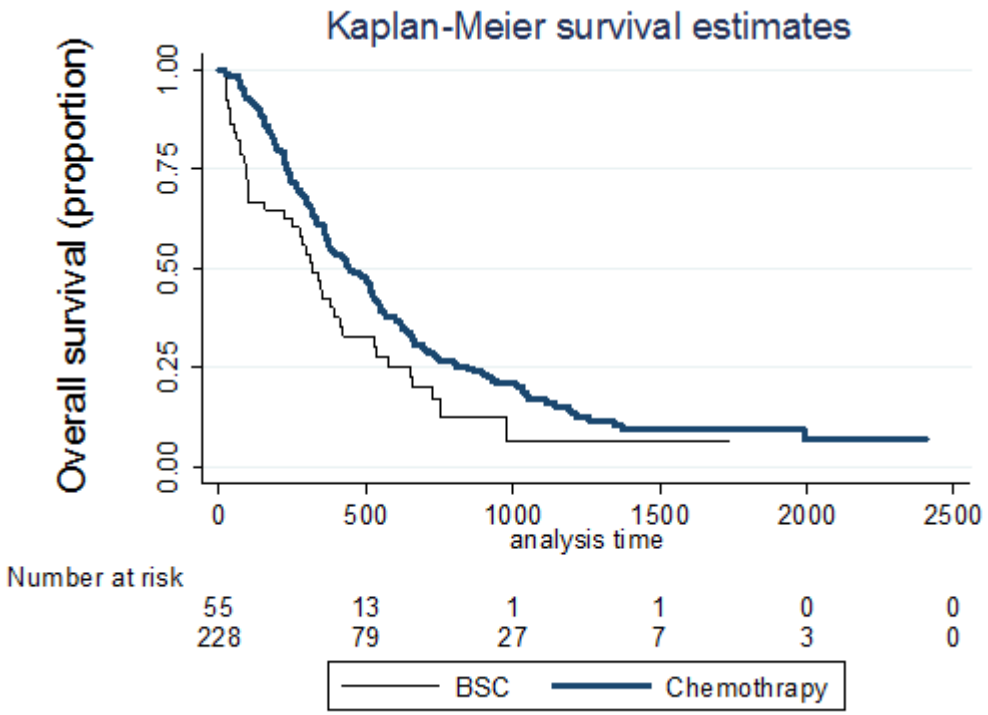
Abbreviations: N, number; OS, overall survival; CI, confidence interval; NE, not estimable; PS, Eastern Cooperative Oncology Group performance status; PEM, pemetrexed.

Figure 1 Patient flow diagram



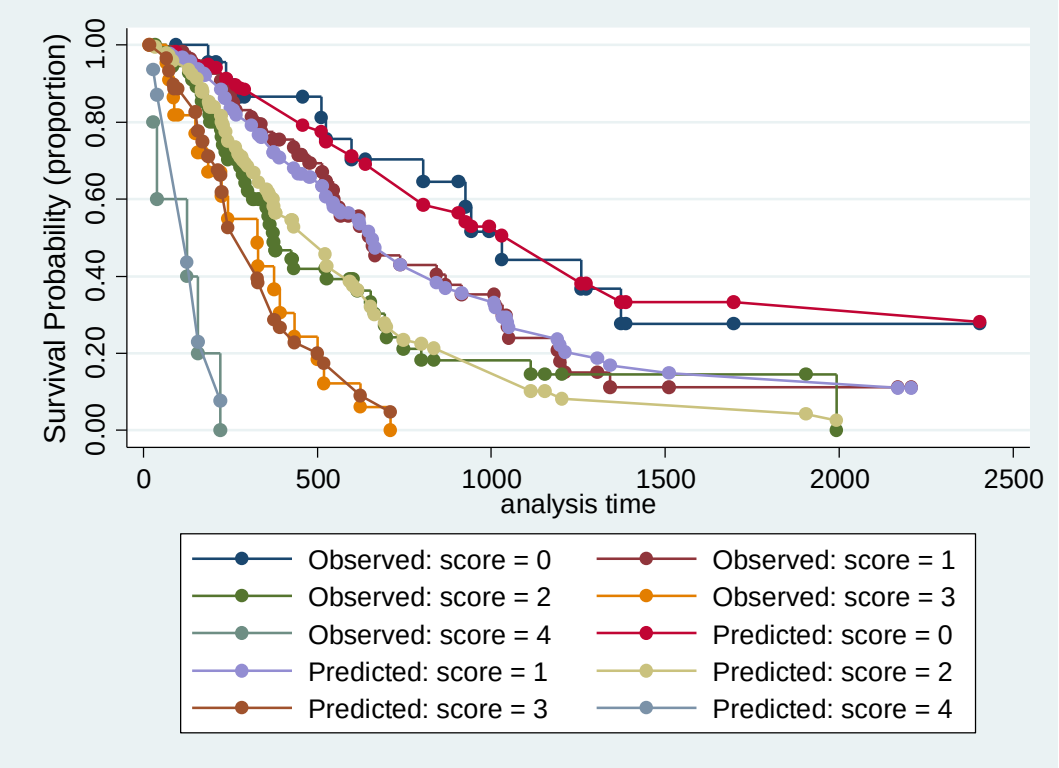
Abbreviations: N, number; MPM, malignant pleural mesothelioma; BSC, best supportive care.

Figure 2 Survival curve (days)



Abbreviations: BSC, best supportive care;

Figure S1 Calibration Kaplan-Meire curve of the rPHS index for chemotherapy group



Abbreviations: BSC, best supportive care;

Figure S2 Cox-Snell Residuals Graph

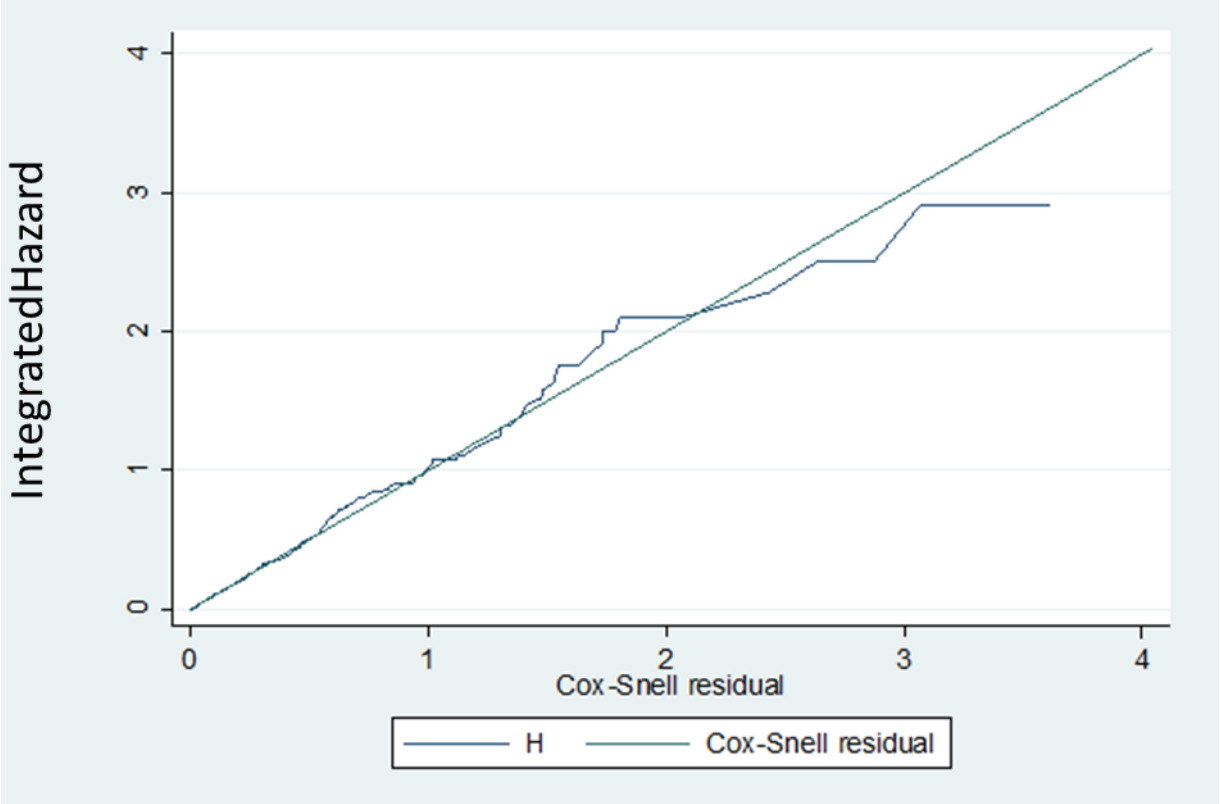


Figure S3 Cumulative hazards curves for the pemetrexed (CTx) group